Visible-Light-Mediated Achmatowicz Rearrangement

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Supporting Information

ABSTRACT: Visible-light-mediated photoredox catalysis is a viable method to access highly reactive intermediates from cheap, readily available, and shelf-stable reagents to perform clean chemical transformations. Here, we report the first photoredox-catalyzed Achmatowicz reaction of furfuryl alcohol derivatives to produce functionalyzed dihydropyranones while only forming easily separable NaHSO₄ as a byproduct. The water solubility of the byproduct facilitates direct Boc-protection of the resulting hemiacetal without the need for column purification. The reaction is very robust and permits the use of various aqueous solutions and light sources including sunlight.

The furan ring serves as a precursor to 1,4-dicarbonyls,1 cyclopentanones,2 and carboxylic acids,3 in organic synthesis. Its molecular complexity can be readily increased via Diels–Alder chemistry.4 Furfuryl alcohols, a class of 2-substituted furan molecules, are a precursor to highly ornamented dihydropyranones via the Achmatowicz rearrangement.5

The rearrangement of furfuryl alcohols to dihydropyranones, first reported by Cavill et al.6 and later popularized by Achmatowicz,7 relies on stoichiometric bromine in methanol, followed by a separate acid catalyzed hydrolysis step (Scheme 1A). To avoid the use of elemental bromine, alternative methods were developed employing either meta-chloroperbenzoic acid (m-CPBA)8 or the bromine surrogate N-bromosuccinimide (NBS)9 (Scheme 1B). However, these reaction conditions produce stoichiometric amounts of organic byproducts. Singlet oxygen, produced with the help of a photosensitizer, is trapped by the furan moiety via a Diels–Alder-type reaction to form a trioxolane intermediate that necessitates the use of stoichiometric triphenylphosphine10 or dimethyl sulfoxide11 for selective decomposition (Scheme 1C).12 Oxone with catalytic amounts of bromide can affect the transformation.13 While the water solubility of the oxidant byproducts greatly facilitated purification and demonstrated greater sustainability than the aforementioned conditions, the method requires low temperatures and exhibits diminished yields unless tetrahydrofuran (THF) is employed as solvent (Scheme 1D), presenting a safety risk due to its proclivity to form peroxides.

Similar to photosensitized reactions, visible light photoredox catalysis is an attractive method of activation, as solar energy is the most abundant renewable energy source and a traceless reagent.14 Polypyridyl complexes are applied as photoredox catalysts to a wide range of transformations in different fields.15 In the context of this work, tris(bipyridine)ruthenium(II) [Ru(bpy)₃]²⁺ has been used extensively in combination with sodium persulfate for the photoinduced oxidation of water.16 However, this combination has found limited applications in the field of organic chemistry.17,18 We hypothesized that persulfate radicals, selectively generated using [Ru(bpy)₃]²⁺, could represent a nonflammable, less toxic, and affordable stoichiometric oxidant to generate dihydropyranones while producing water-separable byproducts in industrially suitable solvents (Scheme 1E).19

In the course of our initial studies we found that the stability of 2-substituted furfuryl alcohols varied greatly. Therefore, we sought to develop a two-step process toward dihydropyranones.

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Scheme 1. Oxidative Rearrangement of Furfuryl Alcohols20

(A) Original Conditions (Cavill/Achmatowicz)

(B) Bromine Alternatives

(C) Singlet Oxygen

(D) In situ Bromine Formation

(E) This work: Photoredox mediated oxidative rearrangement

- Visible Light Driven
- 14 Examples (44-89% 2-Step Yield)
- Only Aqueous Byproducts Generated
- Robust Reactivity

(m-CPBA)⁸ or the bromine surrogate N-bromosuccinimide (NBS)⁹ (Scheme 1B). However, these reaction conditions produce stoichiometric amounts of organic byproducts. Singlet oxygen, produced with the help of a photosensitizer, is trapped by the furan moiety via a Diels–Alder-type reaction to form a trioxolane intermediate that necessitates the use of stoichiometric triphenylphosphine¹⁰ or dimethyl sulfoxide¹¹ for selective decomposition (Scheme 1C).¹² Oxone with catalytic amounts of bromide can affect the transformation.¹³ While the water solubility of the oxidant byproducts greatly facilitated purification and demonstrated greater sustainability than the aforementioned conditions, the method requires low temperatures and exhibits diminished yields unless tetrahydrofuran (THF) is employed as solvent (Scheme 1D), presenting a safety risk due to its proclivity to form peroxides.

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The high yielding, clean reaction of lithiated furan with carbonyls was exploited to generate crude substituted furfuryl alcohols to be utilized directly in the designed photoredox reaction.

Treatment of freshly distilled furan with n-butyllithium generated the 2-lithiated species, which was trapped using cyclohexanone. Aqueous workup and concentration afforded crude furfuryl alcohol 1a, which was taken up in a DMSO/MeCN mixture (1:1), combined with sodium persulfate (1.05 equiv) and Ru(bpy)3Cl2·6H2O (0.5 mol %) in water, and degassed with argon. This solution was irradiated with white light (red/green/blue LEDs), and complete conversion was observed in 1 h (Table 1, entry 1). This three-solvent mixture is necessary because water/DMSO mixtures led to the visibly poor solubility of some furfuryl alcohol substrates, and water/MeCN mixtures led to poor solubility of the persulfate salt. Additionally, solvent mixtures consisting of low proportions of water reacted slower, in good agreement with reports of lower yields of [Ru(bpy)3]3+ decomposition of a trioxolane intermediate.24

Réactions were performed on a 0.5 mmol scale of crude material with respect to the starting carbonyl compound. Starting material (1a) to product (2a) ratios were determined by 1H NMR analysis of 0.1 mL of the crude reaction mixture in 0.4 mL of d6-DMSO; small quantities are indicated by trace (<1:20). See Supporting Information for detailed reaction procedures. A known photosensitizer for singlet oxygen production 23 and responsible for the formation of this side product due to decomposition of a trioxolane intermediate.
the desired product was obtained in very good to excellent isolated yields over two steps. Substrate 1g suffered from unselective reactivity, where the α,β-unsaturated cyclopentanone (Piancatelli product) was isolated in 14% yield. The conditions tolerated aromatic halides (1h) and esters (1i), yielding the product in 85% and 65% yield, respectively. Compound 2k was isolated as a white solid in just 58% yield due to the instability of the more thermodynamically favorable keto-form (see Supporting Information for details). Protected alcohol 2m was obtained in 72% yield, with no isolated side products suggesting no oxidative cleavage of the benzyl group.

Streit–Volmer analysis revealed an oxidative quenching pathway, where [Ru(bpy)]^{2+} is quenched by persulfate to generate sulfate and a sulfate radical (Scheme 3). We propose that the oxidation of the furan ring closes the catalytic cycle, and subsequent combination with the sulfate radical generates intermediate 3, where x is either SO₄⁻ or the hydrolyzed sulfate (x = OH). Addition of water to the oxocarbonium, followed by the loss of x, furnishes the product 2. No intermediates were observed by mass spectrometry or NMR spectroscopy, suggesting these structures are short-lived.

To showcase the benefits of the developed Achmatowicz conditions, we targeted Boc-protected dihydropyranone 2n, an intermediate in the de novo synthesis of monanchorin (Scheme 4). Lithiation of furan, followed by trapping with hexanoyl and aqueous workup, yielded furfural alcohol 1n. This crude material was subjected to our photoredox conditions, which cleanly provided dihydropyranone 2n after another aqueous workup. Protection of the crude hemiacetal was achieved using di-tert-butyl dicarbonate, triethylamine, and catalytic [Ru(bpy)_3]^{2+} for fruitful discussions.

**REFERENCES**


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